JOURNAL OF ANIMAL SCIENCE
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J ANIM SCI 2013, 91:3564-3573.
doi: 10.2527/jas.2012-5911 originally published online June 4, 2013

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The change in differing leukocyte populations during vaccination to bovine respiratory disease and their correlations with lung scores, health records, and average daily gain[1,2,3]

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ABSTRACT: Bovine respiratory disease (BRD) is the most economically important disease in U.S. feedlots. Infection can result in morbidity, mortality, and reduced average daily gain. Cheap and reliable genetic methods of prediction and protection from BRD would be highly advantageous to the industry. The immune response may correlate with BRD incidence. Cattle (n = 2,182) were vaccinated against common viral and bacterial pathogens of BRD. Two blood samples were collected, one during booster vaccination and one 21d later, enabling 3 phenotypes for each trait [prebooster (pre), postbooster (post), and delta (post minus pre)]. From the blood samples innate and adaptive responses [counts of white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, and basophils] were measured. In addition, feedlot ADG and binary traits [health records (HR; 0 = healthy, 1 = ill) and lung scores (LS; collected at harvest; 0 = no lesions, 1 = lesions)] were also recorded. Traits ADG, HR, and LS have all been significantly correlated with infection to BRD. In this investigation we aimed to find correlations between the immune response and ADG, HR, and LS to find an easily measurable trait that would be a good predictor of BRD resistance after vaccination. The results showed an average positive delta for the innate immune response (eosinophils, basophils, neutrophils), whereas the adaptive immune response had an average negative delta (lymphocytes). Overall, we discovered that the immune responses had moderately high heritabilities (h^2; lowest: delta monocytes, 0.21 ± 0.05; greatest: pre lymphocytes: 0.5 ± 0.05), with lymphocytes having the greatest h^2 throughout the study ($h^2 \geq 0.41$). All genetic correlations were calculated using bivariate REML models. Although LS did not significantly correlate with any of the immune phenotypes, both ADG (post lymphocytes, -0.24 ± 0.12) and HR (pre eosinophils, -0.67 ± 0.29; delta WBC, -0.5 ± 0.24, and delta lymphocytes, -0.67 ± 0.21) did. All the significant genetic correlations with HR were negative; resistance to BRD appears to be a function of greater delta lymphocytes and WBC. The increase in eosinophils may potentially link its role in decreasing lymphocytes. These results may enable producers to predict if revaccination, quarantine, and breeding of animals is required to reduce the incidence of BRD postvaccination. In addition, immunological phenotypes maybe used to aid genomic selection indices to select animals with greater rates of protection after BRD vaccination.

Key words: beef cattle, bovine respiratory disease, genetic correlation, genetics, immune response, immunology

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J. Anim. Sci. 2013.91:3564–3573
doi:10.2527/jas2012-5911

INTRODUCTION

Bovine respiratory disease (**BRD**) is the most costly disease in U.S. beef cattle; infection can result in morbidity, mortality, and reduced ADG, causing the value of a carcass to decrease (Irsik et al., 1996; Griffin, 1997; Fulton, 2009). When treatment is also considered, costs can increase rapidly (McNeill et al., 1996; Faber et al., 1999). The estimated heritability of

[1]The authors acknowledge S. Nejezchleb, S. Bierman, C Felber, J. Schulte, T. Gramke, T. Sorensen, and S. Watts for technical assistance and sample collection, the U.S. Meat Animal Research Center cattle operations staff for animal handling, and C. Yates for secretarial support.

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Received September 27, 2012.
Accepted April 30, 2013.

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BRD is low (Muggli-Cockett et al., 1992; Snowder et al., 2005; Schneider et al., 2010); however, it is likely underestimated because of field and observational phenotypes being used (Bishop and Woolliams, 2010). Because of direct and indirect costs associated with treating BRD infection, methods to genetically select or manage animals for increased resistance would be beneficial. By concentrating on correlated component traits, methods such as breeding for increased disease resistance and genetic prediction are possible.

The immune response is highly complex with many components of both the innate and adaptive responses needed to confer immunity after infection or vaccination. White blood cell counts (**WBC**) and counts of white blood cell types (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) are objective measures of innate or adaptive immunity. Measurement of these immune response variables in response to respiratory disease vaccinations could provide an objective measure for the potential of an animal for resistance to BRD.

Lung score (**LS**), health records (**HR**), and ADG have all been used as measures or correlates of BRD incidence (Wittum et al., 1996; Thompson et al., 2006; Schneider et al., 2009). Thus, we investigated all 3 for potential genetic correlations with the immune response. Correlated traits would allow us to understand if the immune response at the end of vaccination is indicative of resistance to BRD or changes in ADG.

Within this study we show that the immune traits (blood phenotypes) change significantly during the time course. We also discover significant correlations between the blood phenotypes and ADG, HR, and LS.

MATERIALS AND METHODS

Animals were raised in conformation with the Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (FASS, 1999), and their care was approved by the U.S. Meat Animal Research Center (**USMARC**) Animal Care and Use Committee.

Phenotypes were collected from 2,182 cattle born in 2008, 2009, and 2010 from the USMARC Germ Plasm Evaluation (**GPE**) herd. The phenotypes were measured at 2 time points during vaccination with 2 multipurpose vaccines. The vaccines offered protection against both viral (BRSV, IBR, PI3, BVD I, and BVD II) and bacterial (such as *Pasteurella haemolytica*) components of BRD. The measured phenotypes were the counts, within whole blood, of WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. In addition to the blood-based phenotypes, HR, LS, and feedlot ADG were also measured.

Animals and Pedigree

Data were collected from animals in advanced generations of the USMARC GPE herd, Clay Center, Nebraska. This particular GPE subset was a product of multiple-sire matings of crossbred cows to F1 bulls of varying half-blood composition. The resulting animals used within this study consisted of variable fractions of 9 breeds: Angus, Hereford, Red Angus, Brahman, Charolais, Gelbvieh, Limousine, Simmental, and MARCIII composite (1/4 Angus, 1/4 Hereford, 1/4 Red Poll, 1/4 Pinzgauer).

As part of a separate project, calves were genotyped for approximately 50,000 SNP markers using the Illumina BovineSNP50 (Illumina Inc., San Diego, CA). Resulting genotypes were used to assign sires to their progeny. By subtracting the genotypes of the candidate animal with each potential parent (in a stepwise manner), the parent of the candidate animal can be predicted; smaller values (when all 50,000 SNP differences are summed) indicate paternity. We excluded paternity if values were greater than 0.05%. If more than 1 sire was eligible, the sire with the smallest value was chosen.

Vaccination Schedule

Initial vaccination was at prebreeding (average age = 60 d). The booster vaccination was administered at preconditioning. The average age of the calves at the booster vaccination was 139 d (with a SD of 17 d).

All animals were vaccinated in accordance with the manufacturer's guidelines. Each animal was administered 2 mL intramuscularly (for both initial and booster vaccinations) of Merck Vista 5 SQ and Vista Once SQ (years 2008 and 2009; Merck Inc., Summit, NJ) or Pfizer Bovi-Shield Gold 5 and One Shot Ultra 8 (animals born in 2010; Pfizer Inc., New York, NY). The vaccines used offered protection from common viral and bacterial components that cause BRD. Only One Shot Ultra 8 contained an adjuvant, Stimugen (Pfizer Inc.).

Phenotypes

Binary Traits. Both HR and LS were analyzed as binary threshold traits. The HR were collected from weaning (165 ± 17 d) to slaughter. The monitoring period for BRD began when animals were weaned into the USMARC feedlot 21 d after the booster vaccination. Animals were not given therapeutic antibiotics during the feeding period, unless there was an outbreak situation. All animals were monitored for respiratory disease and illness by trained cattlemen; cattle were diagnosed on the basis of the observation of multiple symptoms, including lethargy, nasal discharge, isolation from other animals, respiration rate, and body temperature (after being removed from pen for treatment). Cattle not diagnosed with BRD-like symp-

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toms between vaccination and slaughter were coded as 0 for analysis. Cattle that had symptoms sufficient for BRD diagnosis postweaning were assigned a 1.

Lung scores were conducted by observing the percentage of the lung surface containing lung lesions postmortem (similar to the system designed by D. Griffin, University of Nebraska–Lincoln, personal communication). Briefly, lungs were inspected visually at an abattoir at line speed (~360 carcasses/h) by a veterinarian trained to observe lung lesions. Although lungs were scored on a multipoint scale depending on severity (percent of lung with lesions), preliminary analyses showed no additional information was garnered by analyzing the multinomial scale. Therefore, all animals with any lung lesions were coded as a 1, whereas animals with no lesions present were coded as 0.

Average Daily Body Weight Gain. The ADG was calculated as the linear regression coefficient of BW on age of the animal at multiple time points (at least 3 time points for each animal) from weaning through final (preharvest) BW.

Blood Collection and Blood Analysis. Initial blood samples (25 mL) were collected concurrently with the administration of the first booster vaccination at preconditioning. A second blood sample (25 mL) was collected 21 d later at weaning. Whole blood was collected by jugular venipuncture, and 1 mL was deposited into 2-mL screw cap tubes containing potassium EDTA as an anticoagulant. Before analysis on a Hemavet CDC Mascot veterinary hematology analyzer (CDC Technologies, Oxford, CT), the samples were brought to room temperature and stirred for at least 15 min. Data from the analyses were transferred to spreadsheets using WinWedge Pro software (Taltech Inc., Philadelphia, PA). Delta measurements were obtained from the subtraction of the prebooster phenotypes from the postbooster phenotypes. Measurements of WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils were used as phenotypes (all measured in k/μL). Red blood cell phenotypes were also measured but not used as an indicator of immune function.

Statistical Analysis

Software (ASREML; Gilmour et al., 2009) was used for REML estimates of all (co)variance components. Heritability for each trait was estimated using a univariate REML model. For all traits, the model included birth location and mating group by year of birth (CG) and sex (S) as fixed effects; β_1, the linear regression on the expected level of heterosis h (heterosis: min = 0, max = 1, average = 0.78); β_2, the linear regression on birth date b; a, the random effect of animal, a ~ N(0, $\mathbf{A}\sigma^2_g$), where **A** is the numerator relationship matrix; and eijk, the residual error, e ~ N(0, $\mathbf{I}\sigma^2$p):

Table 1. Means and SD of traits measured pre- and postbooster vaccination and the changes between them (delta)

	Prebooster		Postbooster		Delta	
Trait[1]	Mean	SD	Mean	SD	Mean	SD
WBC	10.44	2.76	10.39	2.24	-0.04	2.76
NE*	2.89	1.25	3.03	1.16	0.15	1.42
LY*	5.97	1.74	5.5	1.34	-0.47	1.54
MO	0.65	0.27	0.64	0.23	0	0.30
EO*	0.89	0.50	1.15	0.60	0.26	0.67
BA*	0.04	0.05	0.07	0.09	0.03	0.10

[1]Traits are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA). An asterisk (*) next to the trait name indicates that the pre- and postbooster phenotype measurements are significantly different ($P < 0.01$).

$$Y_{ijk} = \mu + CG_i + S_j + \beta_1 h + \beta_2 b + a_k + e_{ijk.}$$

Breed composition was included in the model using genetic founder group effects (Westell et al., 1988). Bivariate REML models were used to calculate the genetic correlations between ADG, HR, and LS with the blood phenotypes. Because of the binary nature of HR and LS, a probit link function was used; to estimate the genetic correlation of these 2 traits, 1 of the 2 variables was fitted as linear. As results did not vary on the basis of which trait was linear, we show results from fitting LS as linear. The same fixed effects were fitted in bivariate models and univariate models. Relationships among the delta measurements were derived using a 6-trait multivariate model. A *t* test using the SE of the correlation coefficient was used to calculate the correlation *P*-values.

RESULTS

Trait Overview

The blood phenotypes are summarized in Table 1, with "**pre**" phenotypes highlighting concentrations at the point of booster vaccination and "**post**" phenotypes highlighting concentrations at 21 d after booster vaccination. Although the **delta** measurements (post phenotype minus pre phenotype; Table 1) are small and even negative (with 2 of the 6 showing a decrease), *t* tests show highly significant differences between pre vs. post ($P < 0.01$), with the exceptions of WBC and monocytes, which were not significant ($P > 0.05$). Average ADG was 3.15 (SD = 0.49), whereas HR and LS had averages of 0.13 and 0.79, respectively.

Table 2 shows the means for each blood phenotype measure relative to HR and LS. All the phenotypes that are significantly different for HR are also significantly different when grouped by lung score (pre and delta lymphocytes and pre and post basophils; Table 2). In addition, the concentrations of pre WBC and delta WBC are also significantly different between the groupings of

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Table 2. Mean and standard deviation for blood phenotypes measured pre- and postbooster vaccination and the changes between them (delta) when separated by health record and lung score categories

	Health Records					Lung Score				
Trait[1]	0[2]	SD[3]	1[4]	SD	0 vs. 1[5]	0	SD	1	SD	0 vs. 1
Pre_WBC	10.40 (1,882)	2.83	10.68 (277)	2.24		10.67 (429)	2.16	10.32 (1,573)	2.95	<0.01
Post_WBC	10.43 (1,887)	2.25	10.19 (283)	2.15		10.38 (432)	2.32	10.43 (1,584)	2.12	
Delta_WBC	0.06 (1,897)	3.06	-0.27 (284)	2.89		-0.22 (433)	2.42	0.19 (1,590)	3.43	<0.01
Pre_NE	2.88 (1,882)	1.25	2.93 (277)	1.23		2.89 (429)	1.16	2.88 (1,573)	1.39	
Post_NE	3.05 (1,887)	1.15	2.94 (283)	1.19		3.01 (432)	1.20	3.05 (1,584)	1.09	
Delta_NE	0.17 (1,897)	1.47	0.07 (284)	1.40		0.14 (433)	1.33	0.19 (1,590)	1.61	
Pre_LY	5.93 (1,882)	1.76	6.22 (277)	1.57	<0.01	6.24 (429)	1.47	5.89 (1,573)	1.67	<0.01
Post_LY	5.51 (1,887)	1.34	5.46 (283)	1.37		5.54 (432)	1.36	5.50 (1,584)	1.25	
Delta_LY	-0.40 (1,897)	1.71	-0.63 (284)	1.64	<0.05	-0.65 (433)	1.39	-0.35 (1,590)	1.64	<0.01
Pre_MO	0.65 (1,882)	0.27	0.63 (277)	0.22		0.62 (429)	0.22	0.64 (1,573)	0.32	
Post_MO	0.64 (1,887)	0.23	0.64 (283)	0.22		0.63 (432)	0.22	0.65 (1,584)	0.22	
Delta_MO	0.00 (1,897)	0.31	0.02 (284)	0.29		0.01 (433)	0.24	0.02 (1,590)	0.40	
Pre_EO	0.90 (1,882)	0.50	0.87 (277)	0.48		0.88 (429)	0.39	0.86 (1,573)	0.64	
Post_EO	1.15 (1,887)	0.61	1.09 (283)	0.54		1.14 (432)	0.58	1.16 (1,584)	0.56	
Delta_EO	0.26 (1,897)	0.68	0.24 (284)	0.62		0.26 (433)	0.60	0.30 (1,590)	0.79	
Pre_BA	0.042 (1,882)	0.06	0.035 (277)	0.03	<0.01	0.03 (429)	0.04	0.04 (1,573)	0.09	<0.05
Post_BA	0.07 (1,887)	0.09	0.06 (283)	0.07	<0.05	0.06 (432)	0.08	0.07 (1,584)	0.07	<0.05
Delta_BA	0.03 (1,897)	0.10	0.02 (284)	0.07		0.03 (433)	0.08	0.03 (1,590)	0.10	

[1]All names have been standardized. Abbreviations of traits are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA), where pre_ = trait measured when booster vaccinations were administered, post_ = trait measured 21 d after booster vaccinations, and delta_ = post time point minus pre time point.

[2]Here 0 = the mean average of all animals with a 0 for diagnosis (animal remained healthy after vaccination) or lung lesion (no damage to lung). The number in parentheses is the number of animals used to make the observation.

[3]The SD of the measured trait.

[4]Here 1 = the mean average of all animals with a 1 for diagnosis (animal diagnosed with respiratory illness after vaccination) or lung lesion (damage to lung). The number in parentheses is the number of animals used to make the observation.

[5]Here 0 vs. 1 = *P*-value from a 2-tailed *t* test between 0 and 1 of diagnosis or lung lesion. If no value is entered, $P > 0.05$.

lung scores (Table 2). The counts for each phenotype, split by HR and lung score, are also shown in Table 2, where the minimum count for HR was 227 (HR = 1, pre phenotypes). The minimum count for lung score was 429 (lung score = 0, pre phenotypes).

The counts for the 2 binary traits combined are shown in Table 3. It would appear that the diagnosis of a healthy animal with no BRD was accurate during this study. Accordingly, 86.1% of animals that did not have lung lesions had no previous diagnosis. Indeed, of those diagnosed, 76.5% had lung lesions. However, the specificity of the lung lesions as a measure of clinical BRD symptoms appeared low, as animals with lung lesions generally had no diagnosis records (87.7%, Table 3). The 2 traits (LS and HR) are very poor predictors of each other.

Heritability

Heritability was calculated for each blood phenotype as well as ADG, HR, and LS (Table 4). A wide range of heritabilities was observed in this study (Table 4). The greatest heritability estimated for the pre, post, and delta phenotypes was pre lymphocytes [$h^2 = 0.5$ (0.07); Table 4], whereas the smallest was delta monocytes [$h^2 = 0.21$ (0.05); Table 4]. The concentration of lymphocytes in the whole blood appears to be the most consistently heritable phenotype measured throughout the booster vaccination. Its heritability was estimated above 0.4 for the pre, post, and delta phenotypes. In general, heritability is lower for the delta phenotypes. Lung score and HR both had low heritabilities (h^2 for both <0.1; Table 4), whereas ADG had a moderately high heritability [h2 = 0.44 (0.07)].

Genetic Correlations

To discover the role of the additive genetic variation in maintaining increased concentrations of the blood phenotypes during the booster, genetic correlations were calculated between the pre and post phenotypes (Table 5). All of the correlations, with the exception of

Table 3. Counts of the number of animals with different lung scores cross classified with health records

	Lung Score		
Health Records	0	1	Total
0	373	1395	1,768
1	60	195	255
Total	433	1590	2,023

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Table 4. Heritabilities and additive variance for blood phenotypes measured pre- and postbooster vaccination and the changes between them (delta) and ADG, health records, and lung scores

	Prebooster				Postbooster				Delta			
Trait[1]	h^2	SE	Add_Var[2]	SE	h^2	SE	Add_Var	SE	h^2	SE	Add_Var	SE
WBC	0.47	0.06	3.28	0.52	0.47	0.07	2.28	0.38	0.35	0.06	2.34	0.43
NE	0.44	0.06	0.68	0.11	0.41	0.06	0.55	0.1	0.24	0.05	0.47	0.11
LY	0.50	0.07	1.21	0.19	0.45	0.06	0.74	0.12	0.41	0.06	0.76	0.13
MO	0.28	0.06	0.02	0.00	0.39	0.07	0.02	0.00	0.21	0.05	0.02	0.00
EO	0.45	0.07	0.10	0.02	0.42	0.06	0.14	0.02	0.38	0.06	0.16	0.03
BA	0.23	0.06	0.001	<0.001	0.25	0.06	0.002	<0.001	0.25	0.06	0.002	<0.001
ADG[3]									0.44	0.07	0.08	0.01
Health records[3]									0.07	0.05	0.08	0.06
Lung score[3]									0.06	0.04	0.07	0.05

[1]Traits are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA).

[2]Add_Var = additive variance for each trait.

[3]The delta measurement was not used for ADG, diagnosis, and lung score. These were measured at differing time points, as discussed in the Materials and Methods section.

basophils, differed from 0 ($P < 0.05$). The 3 greatest correlations of WBC, neutrophils, and lymphocytes (0.64 ± 0.07, 0.73 ± 0.08, and 0.67 ± 0.06, respectively; Table 5) were highly significant ($P < 0.01$). Although the average WBC and the lymphocytes delta measurements are negative, they show positive genetic correlations between the pre and post measurements (Tables 1 and 5).

Genetic correlations were estimated (Table 6) between all of the blood phenotypes with ADG, HR, and LS. Of the estimated correlations, 4 were significant (*t* test; $P < 0.05$; Table 6). The majority of phenotypes (with the exceptions of pre neutrophils, post eosinophils, delta monocytes, delta eosinophils, and HR) were negatively correlated with ADG. However, the only 1 of these correlations that was significant was between ADG and post lymphocytes (-0.24 ± 0.12), indicating that ADG decreased as post lymphocytes concentrations increased. No significant correlations existed between any blood phenotype and LS. However, 3 phenotypes were significantly correlated with HR (pre eosinophils, delta WBC, and delta lymphocytes; Table 6). The greatest correlation was significant with a *P*-value of less than 0.01 (delta lymphocytes), whereas the other 2 had *P*-values of 0.05 or better (pre eosinophils, delta WBC).

When compared, the genetic correlations of the phenotypes with HR vs. with LS have little similarity. Ten of the 18 correlations calculated did not change direction when the same trait was correlated with HR as opposed to LS (Table 6). However, large SE are present, and little genetic correlation exists between the 2 binary traits (0.16 ± 0.6; Table 6), highlighting the differing magnitudes of correlation between the measured phenotypes and the 2 binary traits.

Genetic correlations of the delta blood phenotypes are summarized in Table 7. In general, the blood phenotypes were highly correlated, with 10 of the 15 possible correlations being significant ($P < 0.05$). With the exception of basophils vs. neutrophils and lymphocytes, all of the significant correlations were positive.

Table 5. Genetic correlations of pre- and postbooster vaccination measurements of blood phenotypes

Trait[1]	Pre vs. post r^2	SE
WBC	0.65***	0.07
NE	0.72***	0.08
LY	0.67***	0.06
MO	0.39*	0.15
EO	0.27*	0.12
BA	-0.12	0.20

[1]Traits are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA).

[2]Pre vs. post *r* = genetic correlation between the prebooster and postbooster trait. *$P < 0.05$; ***$P < 0.001$.

Breed Differences

The models used during this study estimated the effects of each breed in the GPE herd. All breeds showed similar effects throughout the study (Table 8), with few being significantly different from the others for any trait. A notable exception is the *Bos indicus* breed, Brahman, which was significantly different from the other breeds throughout various phenotypes. From all the breeds that compose the GPE herd, Brahman and Hereford elicited significantly different phenotypes the most frequently. No other breeds were significantly different from each other. In addition, the results indicated that no breed had a significant effect on ADG, diagnosis, or lung lesion.

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Table 6. Genetic correlations of blood phenotypes pre- and postbooster vaccination and the changes between them (delta) with ADG, health records, and lung score

	ADG		Health record		Lung score	
Trait[1]	*r*	SE	*r*	SE	*r*	SE
Pre_WBC	-0.05	0.12	0.10	0.26	0.20	0.32
Post_WBC	-0.20	0.12	-0.44	0.24	0.19	0.31
Delta_WBC	-0.14	0.13	-0.50*	0.24	-0.06	0.34
Pre_NE	0.04	0.13	-0.36	0.28	0.10	0.32
Post_NE	-0.10	0.13	-0.52	0.27	-0.19	0.31
Delta_NE	-0.20	0.16	-0.16	0.33	-0.28	0.39
Pre_LY	-0.08	0.12	0.48	0.25	0.21	0.32
Post_LY	-0.24*	0.12	-0.26	0.23	0.56	0.35
Delta_LY	-0.12	0.12	-0.67**	0.21	0.22	0.3
Pre_MO	-0.17	0.17	-0.33	0.33	0.36	0.45
Post_MO	-0.10	0.14	-0.14	0.28	0.50	0.33
Delta_MO	0.00	0.16	0.12	0.32	0.29	0.37
Pre_EO	-0.08	0.13	-0.67*	0.29	-0.03	0.33
Post_EO	0.00	0.13	-0.23	0.27	-0.38	0.32
Delta_EO	0.05	0.13	0.16	0.27	-0.39	0.34
Pre_BA	-0.04	0.18	-0.14	0.35	-0.22	0.43
Post_BA	-0.05	0.15	0.33	0.3	-0.64	0.36
Delta_BA	-0.04	0.15	-0.23	0.27	-0.52	0.37
Lung score	-0.15	0.33	0.16	0.59		
Diagnosis	0.25	0.27				

*$P < 0.05$; **$P < 0.01$.

[1]Traits are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA), where pre_ = trait measured when booster vaccinations were administered, post_ = trait measured 21 d after booster vaccinations, and delta_ = post time point minus pre time point.

Table 7. Genetic correlations[1] between changes in (delta) blood phenotype pre- and postbooster vaccination

Delta blood	Delta blood phenotypes					
phenotypes[2]	WBC	NE	LY	MO	EO	BA
WBC		0.05	0.04	0.13	0.10	0.15
NE	0.86***		0.11	0.19	0.15	0.18
LY	0.86***	0.75***		0.14	0.12	0.12
MO	0.37**	-0.05	0.09		0.08	0.12
EO	0.43***	0.17	-0.05	0.87***		0.06
BA	-0.10	-0.36*	-0.48***	0.71***	0.81***	

[1]Below the diagonal shows the genetic correlation coefficient; above the diagonal shows the SE. *t* tests were conducted to obtain *P*-values (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

[2]The blood phenotypes are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA).

DISCUSSION

This investigation aimed to discover correlates of immunity significantly associated with BRD incidence. Discovering correlates affecting BRD incidence after vaccination has the potential to help producers alter vaccination schedules, isolate animals that are vulnerable to infection, and, most importantly, reduce the incidence of BRD in a herd by providing heritable targets for genetic and, eventually, genomic selection. Further, by defining accurate immunological phenotypes, vaccinologists may, in turn, be able to design vaccines that benefit weak responders by investigating the immune responses of successfully immunized animals. This investigation monitored the immune response of a herd of crossbred cattle during the final stage of vaccination to both viral and bacterial causes of BRD. The immune response, as measured by counts of white blood cell populations, was found to be highly variable and heritable during this period, which has been highlighted in different herds using different vaccines/immunizations and phenotypes (Kalina et al., 2005; Leach et al., 2010, 2012). Using genetic models to attribute the phenotypic variation to genetic components has enabled this study to suggest possible correlates to immune responses, which may allow selection for animals that are more resistant to BRD after vaccination.

Both the innate and the adaptive immune responses play a role in vaccination to ensure that a long-lasting immunologic memory is formed. Although the immune response variables measured in the current study were nonspecific to the vaccines used, they do highlight the processes of the immune system during vaccination to BRD. Further, as similar response profiles were recorded each year of vaccination, the results suggest that the responses observed during this study were elicited by the vaccines used.

The innate immune system has evolved to target and remove bacterial and viral pathogens. Detection of such pathogens, within the innate immune system, is nonspecific. Thus, cells of the innate immune system have evolved receptors such as pathogen recognition receptors to detect pathogen-associated molecular patterns (Werling and Jungi, 2003; Akira et al., 2006) and Fc receptors to detect antibody-bound viral and bacterial particles (Janeway et al., 2005). Three cell types of the polymorphonuclear cell family, which contribute to the innate immune response, were measured in the current study (neutrophils, basophils, and eosinophils). All 3 cell types contain receptors to interact with specific antibody isotypes and cytokines released during an immune response (Paape et al., 2003; Ackermann et al., 2010; Tizard, 2012). A significant increase in these cell types was observed in our results after BRD vaccination. Thus, although the lymphocytes response was on average declining, parts of the innate immune system were still increasing. As the half-life of granulocytes is relatively short (Carlson and Kaneko, 1975) and neutrophils are a swift-acting part of the innate immune response, often migrating to the location of infection within 1 h to engage with bacterial pathogens (Paape et al., 2003), we suggest that these cell types were actively engaging either one or both of the vaccines. In addition, a review of the current literature in humans has shown

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Table 8. Predicted breed means for each of the blood phenotypes pre- and postbooster vaccination and the changes between them (delta), ADG, lung score, and health records[1]

Trait[2]	Angus	SE	Hereford	SE	Red Angus	SE	Brahman	SE	Charolais	SE	Gelbvieh	SE	Limousin	SE	Simmental	SE
Pre_WBC	10.66	1.74	10.52	1.70	12.11	1.66	11.07	2.68	12.45	1.75	11.41	1.73	11.73	1.69	10.03	1.78
Post_WBC	10.25	1.46	9.28	1.43	10.44	1.39	11.96	2.24	11.19	1.46	10.91	1.45	10.52	1.42	9.93	1.50
Delta_WBC	-0.59	1.68	-1.39	1.64	-1.77	1.61	0.29	2.49	-1.32	1.69	-0.59	1.67	-1.32	1.64	-0.14	1.72
Pre_NE	2.93	0.81	2.68	0.80	3.13	0.78	2.25	1.24	3.48	0.82	3.15	0.81	2.45	0.79	3.31	0.83
Post_NE	2.63	0.76	2.77	0.74	3.24	0.72	2.45	1.15	2.92	0.76	3.62	0.75	2.36	0.74	3.29	0.78
Delta_NE	-0.29	0.89	0.08	0.87	0.16	0.85	-0.05	1.27	-0.44	0.90	0.47	0.89	-0.04	0.87	0.10	0.91
Pre_LY	5.73	1.02	6.24	1.00	6.71	0.98	7.11	1.59	6.66	1.03	6.49	1.02	7.40	1.00	5.22	1.05
Post_LY	4.97	0.84	4.64	0.82	4.89	0.80	5.31	1.29	5.50	0.84	4.54	0.83	5.77	0.82	4.15	0.86
Delta_LY	-0.82	0.89	-1.68	0.87	-1.89	0.85	-1.94	1.35	-1.22	0.90	-1.97	0.89	-1.70	0.87	-1.10	0.92
Pre_MO	0.68	0.16	0.60	0.16	0.80	0.15	0.79	0.23	0.64	0.16	0.45	0.16	0.71	0.16	0.42	0.16
Post_MO	0.65	0.14	0.46	0.14	0.51	0.14	0.81	0.22	0.50	0.15	0.45	0.14	0.54	0.14	0.34	0.15
Delta_MO	-0.07	0.18	-0.16	0.17	-0.31	0.17	-0.02	0.25	-0.16	0.18	-0.01	0.18	-0.18	0.17	-0.09	0.18
Pre_EO	1.33	0.31	0.98	0.30	1.40	0.29	0.88	0.47	1.61	0.31	1.34	0.30	1.14	0.30	1.10	0.31
Post_EO	1.88^{ab}	0.38	1.36^{a}	0.37	1.67^{ab}	0.36	2.95^{b}	0.58	2.17^{ab}	0.38	2.14^{ab}	0.38	1.75^{ab}	0.37	2.01^{ab}	0.39
Delta_EO	0.51^{a}	0.42	0.35^{a}	0.41	0.25^{a}	0.40	2.00^{b}	0.63	0.53^{ab}	0.42	0.77^{ab}	0.42	0.58^{ab}	0.41	0.88^{ab}	0.43
Pre_BA	0.07	0.03	0.04	0.03	0.07	0.03	0.06	0.05	0.07	0.03	0.04	0.03	0.05	0.03	0.02	0.03
Post_BA	0.11^{a}	0.06	0.06^{a}	0.05	0.09^{a}	0.05	0.32^{b}	0.08	0.11^{a}	0.06	0.12^{a}	0.06	0.10^{a}	0.05	0.14^{ab}	0.06
Delta_BA	0.04^{a}	0.06	0.02^{a}	0.06	0.02^{a}	0.06	0.26^{b}	0.09	0.03^{a}	0.06	0.08^{ab}	0.06	0.05^{a}	0.06	0.11^{ab}	0.06
ADG	3.58	0.46	3.72	0.45	3.76	0.45	3.11	0.55	3.47	0.46	3.43	0.46	3.52	0.45	3.57	0.46
Diagnosis	-3.58	1.23	-2.10	1.15	-3.05	1.18	–4.70	1.52	-3.44	1.23	-3.23	1.20	-2.95	1.18	-3.13	1.21
Lung Score	2.12	1.03	1.19	0.93	0.30	0.92	0.60	1.14	1.03	0.97	1.26	0.95	0.85	0.93	0.70	0.96

[1]Within a row means with different superscripts are different ($P < 0.05$).

[2]The traits are white blood cells (WBC), neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO), and basophils (BA), where pre_ = trait measured when booster vaccinations were administered, post_ = trait measured 21 d after booster vaccinations, and delta_ = post time point minus pre time point.

that eosinophils also play an active role in modulating a Th2-mediated response (Kita, 2011). There is a close resemblance between the bovine and human immune responses (Goddeeris, 1998). Thus, a similar role may be occurring within the current study, with eosinophils having an active part in modulating the role of the lymphocytes during this immune response.

The average decrease in the lymphocytes suggests that the adaptive immune response to the vaccines was declining by the second time point, having had ample time to produce a response with the possibility of immunological memory. However, when investigating the additive genetic correlation between pre and post phenotypes, lymphocytes showed a significant positive correlation. Several animals did increase or maintain lymphocytes concentrations throughout both measurements. These animals may be allocating more resources to immune function (negative correlation with ADG) and are likely less susceptible to BRD (based on negative HR correlation) after vaccination.

Estimates of heritability for BRD infection (using HR or LS) remain low (Muggli-Cockett et al., 1992; Snowder et al., 2005). The low estimates are largely caused by the phenotypes used to record BRD incidence. Bishop and Woolliams (2010) have shown that heritability may be underestimated because broad-based phenotypes (such as the binary traits used in the current study) cannot account for all the different types of pathogens that cause infection. Additionally, there are often errors in coding healthy animals as diseased and diseased animals as healthy. Both misclassifications severely impact the heritability estimated from diagnoses. Indeed, the outcome of this study has also shown low estimates of heritability (0.06 and 0.07 for LS and HR, respectively). The immune response phenotypes were estimated to have much higher heritabilities. However, these responses were measured very accurately during a short time frame (during vaccination, which should elicit an immune response). The higher heritabilities and the magnitude of their genetic correlation with HR suggest these blood phenotypes could be candidates for indicator traits in genetic and genomic evaluations.

During this investigation we aimed to identify measurable immunological phenotypes that significantly changed during vaccination and had a positive effect on BRD incidence. A method we chose to do this tested for significant genetic correlates of ADG, HR (until slaughter), and LS (at harvest) with the immune responses measured.

Although measuring the LS at harvest maybe cost and labor prohibitive, correlations have been reported between lung ultrasonography and respiratory disease in cattle (Rabeling et al., 1998; Flock, 2004). Thus, the use of ultrasonography to detect lung lesions in cattle

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to identify either current or previous interactions with a BRD pathogen is possible. Unfortunately, no significant correlation existed between the lung lesions and the immune responses in this study, suggesting the immune response measures in this study are poor predictors of the propensity of cattle to have long-term lung damage. Many reasons could account for the unexpected nonsignificant correlation. In the current study, the immune response was only measured for a relatively short time course containing only 2 time points. Thus, the change in the immune response may occur before or after the booster vaccination. Another possibility highlights the specificity of the immune phenotypes measured. In the current study, broad blood-based components of both the innate and adaptive immune responses were measured. If a more targeted phenotype (e.g., alveolar macrophages) that plays a role in BRD detection, and possibly pathology, within the lungs (Ackermann et al., 2010) were used, a significant correlation might have become apparent.

The current study found no evidence of a significant correlation between lung lesion and BRD incidence. An issue with the correlation appears to be the crossover between the distributions. For example, 76% of the animals that were diagnosed did indeed have lesions in the lung, which indicates a premise for correlation. However, 87% of animals that had lung lesions were diagnosed as healthy (with respect to BRD). Other studies have shown similar trends with a large number of untreated animals also having lung lesions (38% to 68%;Wittum et al., 1996; Bryant et al., 1999; Thompson et al., 2006; Schneider et al., 2009); however, the percentage we present is considerably greater. Much of the error may have come from the method used to record lung lesions. Other studies used specific areas of the lung to calculate lung lesions. They also used discrete rather than binomial distributions, enabling more power to detect correlations with health trait records. Unfortunately, the current study did not because of the speed required to record lung lesions on a large number of animals. Thus, because of the lack of specificity and the overall trait type (which has low heritability), detecting significant genetic correlation using the techniques outlined in this investigation would require many more animals.

The delta responses of the WBC and lymphocytes were negatively correlated with HR. Thus, selection to increase lymphocytes and WBC deltas should improve BRD health overall after vaccination. The results also showed that animals genetically predisposed to have greater pre lymphocytes concentrations had a greater probability of remaining healthy with respect to BRD. Thus, the successful immunization of animals (within this herd) appears to be a function of a greater concentration of pre lymphocytes and a low rate of decline (or no decline) of WBC and lymphocytes 21 d after the booster vaccination is administered. Potentially, a function of these phenotypes could be used to segregate successfully vaccinated animals from those that need further vaccination or quarantine. Further, breeding programs may be able to add these phenotypes to breeding indices to reduce the overall incidence of BRD within a herd or as target traits in genomic selection given the reduced efficacy of using HR alone.

Producing a delta measurement of lymphocytes (or any of the blood phenotypes used in the current study) requires a significant amount of time, resources, and equipment to accurately quantify cell-type concentrations from blood collected from animals at booster vaccination and 21 d later. With the use of modern genomics this phenotype might not need to be measured every generation (Hayes et al., 2009). If animals are genotyped, markers in the genome can be tested for significant associations with phenotypes (delta lymphocytes in this instance). As a result, selection of favorable cattle in subsequent generations could occur at birth, vastly speeding up generation intervals. We believe that genomic selection shown in the dairy industry (Hayes et al., 2009) would also apply to selection of cattle that respond to vaccines with perceived immunity. Thus, the money spent collecting highly heritable and correlated indicator phenotypes, such as these, would be a valuable investment into the genomic advancement of a herd, reducing the incidence of BRD post vaccination.

Many studies have shown a negative correlation between animals that are “infected with” or “treated for” BRD and ADG even during treatment (Bateman et al., 1990; Jim et al., 1993; Wittum et al., 1996; Thompson et al., 2006; Schneider et al., 2009). The current study, however, discovered the opposite, an insignificant correlation between BRD and ADG. It is likely this relationship depends on the level of BRD affecting the herd; under high challenge, increased immune function may divert energy from growth. Indeed, the current study did have many negative correlations with ADG; however, the only significantly negative correlation was estimated between post lymphocytes and ADG, thereby indicating that as the number of lymphocytes increases, the ADG decreases. Thus, the animals within the herd may have been diverting energy from growth to eliciting immune responses. This will have a negative impact on cost of production (as number of days fed to slaughter will increase). However, from these results we suggest the possibility that any immune response may reduce ADG (nonspecific immune responses were measured during the current study); thus, an immune response elicited from a vaccine at a controlled time point and at a controlled dose should give animals the best possible chance to form immunological memory and minimally affect ADG. Also, the prevalence in the beef industry suggests

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that this lower genetic potential for ADG may be a fair compromise. Further, changes in the age of vaccination may potentially alter the negative correlation. In addition, it appears that HR and, to a lesser extent LS, may be used as a diagnostic tool. For example, the use of the delta lymphocyte phenotype as a correlate for later health relative to BRD may enable producers to target animals that may have responded to BRD vaccination poorly.

The immune response to infection is variable between breeds (Morris, 2007). Further, breed analysis of the incidence of BRD has shown some significant differences between breeds (Snowder et al., 2006). Within the current study the results indicated 1 major difference among the breeds. Brahman was significantly different from all other breeds for at least 1 phenotype, with the exception of Simmental. Thus, the major difference appears to be in the differential way a *Bos taurus* animal elicits an immune response compared with a *Bos indicus*–cross animal. Each significant difference in breed response shows the Brahman breed eliciting a greater response. Further research with more *Bos indicus* breeds (the current study contains only 1) is needed to further validate the differences between the 2 subspecies using these immune variables. However, our results do indicate that animals with a greater number of eosinophils (which was significantly different between breeds) are treated less commonly for BRD post vaccination. Thus, the significant differences between *Bos taurus* and *Bos indicus* may indicate how a favorable immune response is elicited in cattle. These results may also be due to breed-specific heterosis (i.e., greater heterosis for *Bos indicus* crosses) rather than a strict breed effect. However, this herd is not ideal for picking out breed-specific differences as the majority of animals contained within are only a quarter to a half of any 1 breed. This makes breed comparisons difficult and may explain why ADG was very similar across the multiple breeds.

Much is still unknown about the genetic effects behind the immune response. In this investigation we have added to the growing body of research that is currently investigating the genetic effects behind successful vaccination for BRD. We have shown a significant genetic correlation of eosinophils count before booster vaccination with HR after vaccination. We have also shown that changes in WBC and lymphocyte concentrations during the booster phase of vaccination are correlated with the ongoing health of an animal and the potential for genetic selection based on immune response. Further, we have shown that components of the innate immune response appear to be actively increasing during the booster phase, and this also correlates with the health of the animal.

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